

# Advances in the management of hepatorenal syndrome

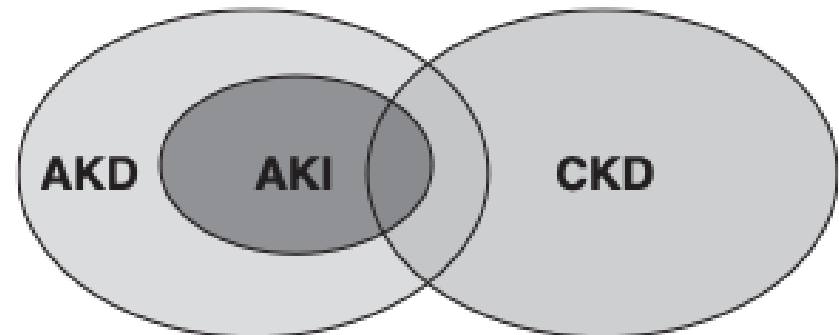
ALEX MYINT MD

# Objectives

- ▶ Define acute kidney injury (AKI) and hepatorenal syndrome (HRS)
- ▶ Discuss treatment strategies in the management of HRS
  - ▶ Emphasis on role of terlipressin
- ▶ Review strategies to prevent HRS

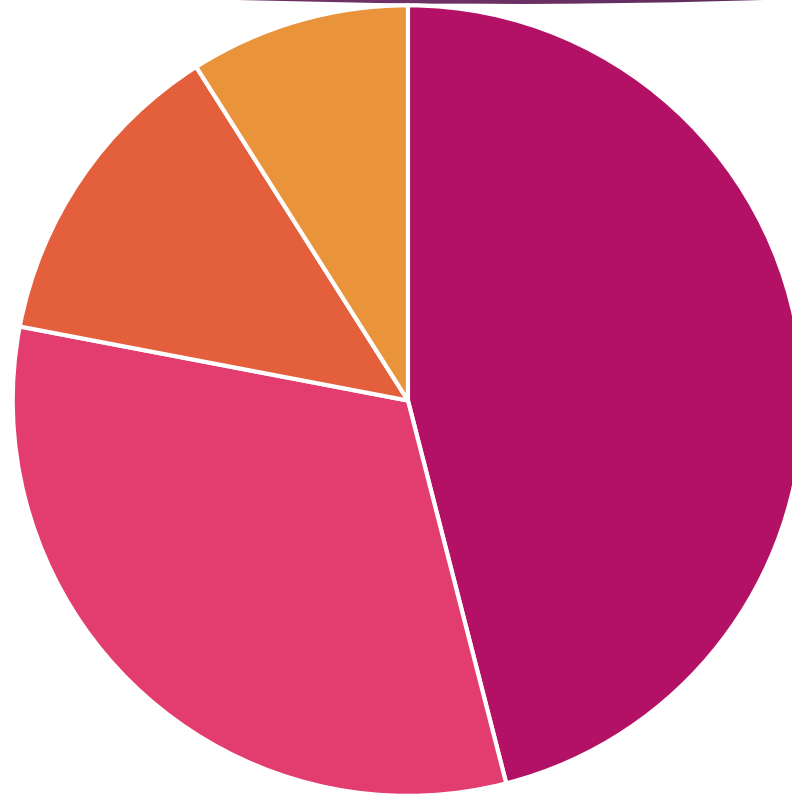
# Defining AKI

- ▶ Increase in serum creatinine  $>0.3\text{mg/dL}$  in 48 hours or  $>50\%$  increase in creatinine within 7 days<sup>1</sup>
- ▶ Common in patients with decompensated cirrhosis<sup>2</sup>
- ▶ Associated with poor prognosis



1. Kidney International. 2012
2. Nadim and Garcia-Tsao. NEJM. 2023.
3. Biggins et al. Hepatology. 2021

# Causes of AKI in cirrhosis



■ Infection ■ Hypovolemia ■ HRS ■ Parenchymal

# Hepatorenal syndrome

- ▶ Clinical syndrome resulting in AKI in patients with cirrhosis in the absence of hypovolemia or significant abnormalities in kidney histology
- ▶ Diagnostic criteria
  - ▶ Cirrhosis with ascites
  - ▶ Presence of AKI
  - ▶ No response to diuretic withdrawal and volume expansion
  - ▶ Absence of shock or other nephrotoxic insult
  - ▶ No signs of structural kidney disease



# Current nomenclature

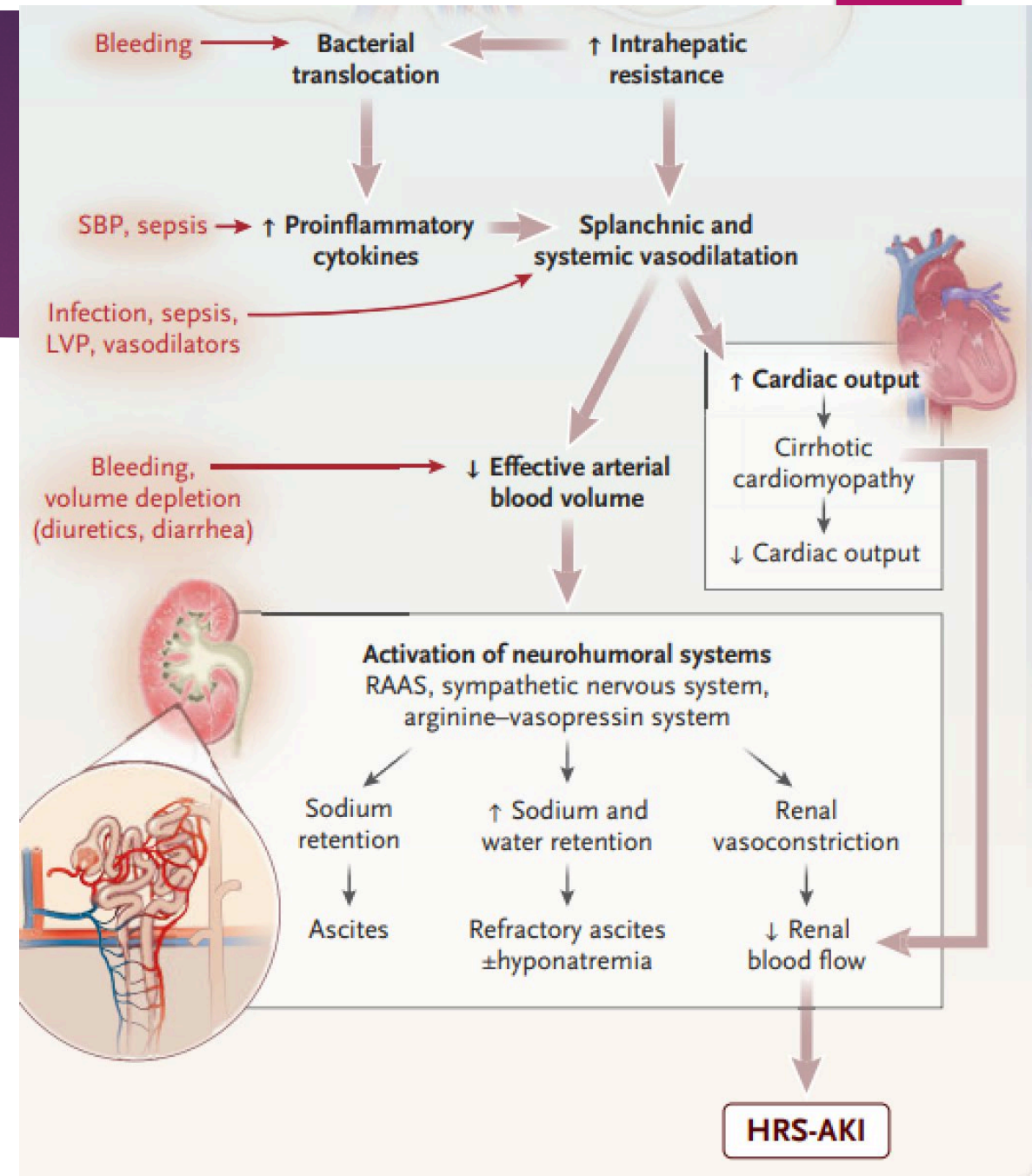
## HRS-AKI

- ▶ Previously known as type 1 AKI
- ▶ Definition previously described
- ▶ Emphasis of this talk

## HRS-CKD

- ▶ Previously known as type 2 HRS
- ▶ Slower progression than HRS-AKI
- ▶ Tends to occur in those with refractory ascites
- ▶ eGFR  $<30$  mL/min/1.73 m<sup>2</sup> for  $>3$  months in absence of other cause

# Why HRS happens



# HRS-AKI Management Strategies

Terlipressin

Norepinephrine

Midodrine/Octreotide

Renal replacement therapy

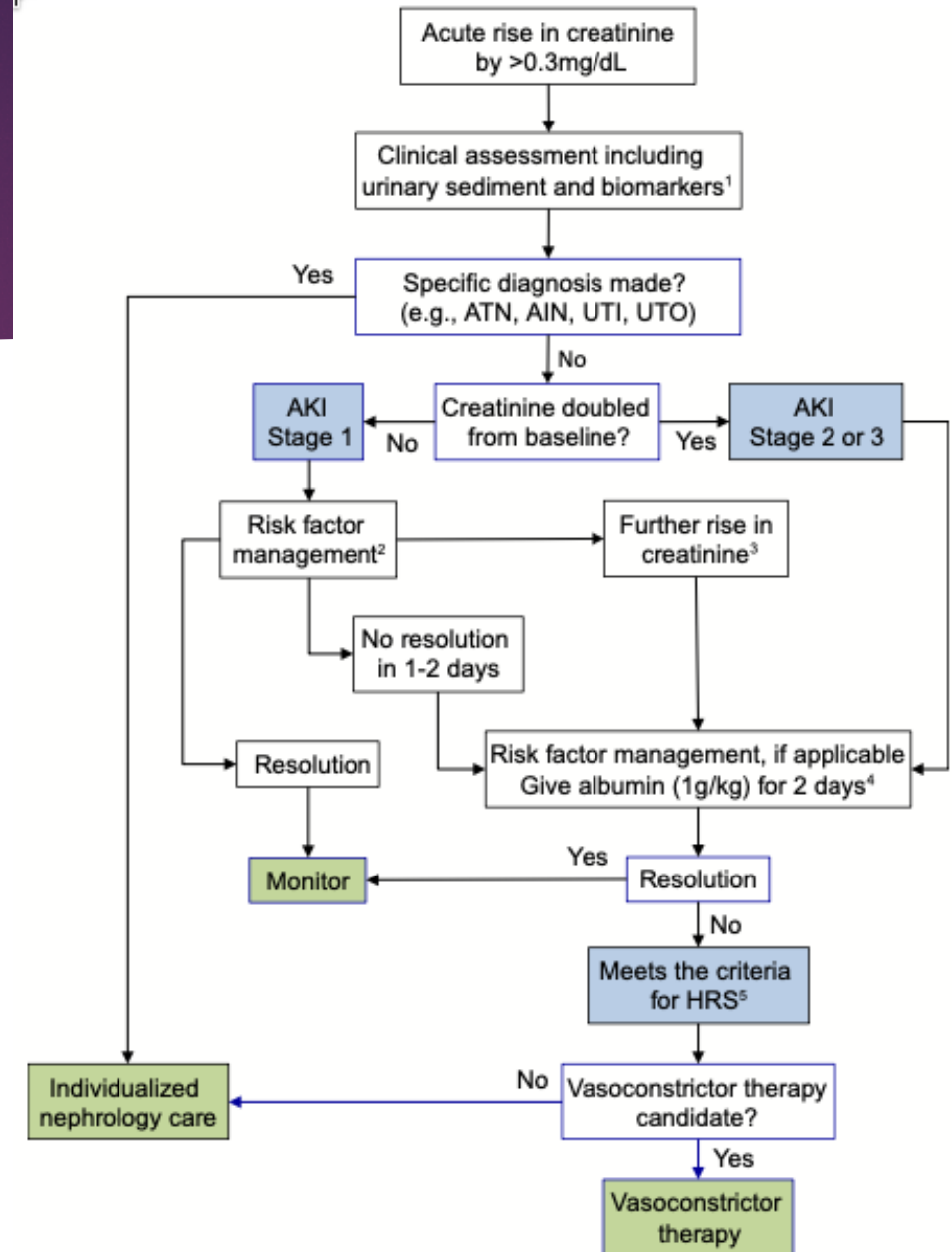
TIPS?

Transplantation



# Goals in HRS-AKI therapy

- ▶ Improve renal perfusion
- ▶ Avoid additional nephrotoxic insults
- ▶ Albumin is a part of all regimens
- ▶ Treat until resolution
- ▶ Bridge to transplant (if possible)



# Terlipressin

- ▶ Vasopressin analogue with vasoconstrictor activity in the splanchnic and systemic vasculature
- ▶ Given as IV infusion for treatment of HRS-AKI
- ▶ Used in Europe as 1<sup>st</sup> line treatment of HRS-AKI, recently approved in US

# CONFIRM Trial

- ▶ RCT of 300 patients with decompensated cirrhosis and HRS-AKI
  - ▶ Randomized 2:1 terlipressin/albumin vs placebo/albumin
- ▶ Treatment associated with increased HRS-AKI reversal, less need for RRT, and short-term survival (10 days after treatment)
- ▶ No improvement in longer term survival

**Table 2. Primary and Four Secondary End Points Included in Multiplicity Adjustment.\***

End Point	Terlipressin <i>number/total number of patients (percent)</i>	Placebo	P Value
<b>Primary end point of verified reversal of HRS†</b>			<b>0.006</b>
Clinical success	63/199 (32)	17/101 (17)	
Clinical failure	121/199 (61)	81/101 (80)	
<b>Competing event‡</b>			
Liver transplantation	10/199 (5)	2/101 (2)	
Death	5/199 (3)	0/101	
<b>HRS reversal with no renal-replacement therapy through 30 days</b>			<b>0.001</b>
Clinical success	68/199 (34)	17/101 (17)	
Clinical failure	116/199 (58)	80/101 (79)	
<b>Competing event‡</b>			
Liver transplantation	10/199 (5)	3/101 (3)	
Death	5/199 (3)	0/101	

# Using terlipressin

- ▶ Give 0.85mg IV every 6 hours x 3 days
- ▶ Reassess on day 4
  - ▶ If <30% improvement, may increase to 1.7mg every 6 hours
  - ▶ If >30% improvement, continue 0.85mg every q 6 hours
  - ▶ If at baseline, discontinue
- ▶ Continue until creatinine <1.5mg/dL x 24 hours or 14 days total
- ▶ Assess ACLF grade and volume status prior to treatment
- ▶ Oxygen saturation monitoring required
  - ▶ Do not start if SpO<sub>2</sub> <90%
  - ▶ Patients require continue pulse oximetry while on treatment
- ▶ Treatment discontinuation may be necessary if ischemia, respiratory failure, or volume overload



# Contraindications/Adverse effects

## Contraindications

- ▶ Hypoxia (SpO<sub>2</sub><90%)/respiratory failure
- ▶ Evidence of ischemia
- ▶ Terlipressin may worsen these
- ▶ ACLF grade 3 associated with higher risk of respiratory failure
- ▶ Creatinine >5 unlikely to benefit

## Additional adverse reactions

- ▶ Abdominal pain
- ▶ Nausea
- ▶ Respiratory failure
- ▶ 12% had adverse events that led to discontinuation

# Norepinephrine

- ▶ Titrated dose to achieve >10mmHg increase in MAP
- ▶ Use when terlipressin not available/contraindications
  - ▶ May be as effective as terlipressin
- ▶ Logistical challenge related to need for ICU bed



An ounce of prevention is worth  
a pound of cure.

”

BENJAMIN FRANKLIN

# Strategies to Prevent HRS-AKI

- ▶ Avoid nephrotoxic medications in at risk patients (NSAIDs, ACE inhibitors, ARBs)
  - ▶ Window period for beta blockers
  - ▶ Judicious use of IV contrast
- ▶ Avoid volume depletion
- ▶ Albumin with large volume paracentesis and during episodes of SBP
- ▶ Provide antibiotics during GI bleed or as SBP prophylaxis, if indicated



# Takeaway points

- ▶ AKI is common in patients with decompensated cirrhosis
- ▶ HRS-AKI is a rapidly progressive condition associated with high mortality
- ▶ Vasoconstrictor therapy to raise MAP (and renal perfusion) can help reverse HRS-AKI but urgent transplant evaluation should be considered
- ▶ Terlipressin was recently approved to treat HRS-AKI
- ▶ Prevention of HRS-AKI is important